EXHIBIT D

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ART UNIT	**PAPER NUMBER**
3992	

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Please find below and/or attached an Office communication concerning this application or proceeding.

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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO 90/007724

PATENT NO. 6,528,784

ART UNI 3992

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified ex parte reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the ex parte reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Order Granting / Denying Request For Ex Parte Reexamination	Control No.	Patent Under Reexamination	
	90/007,724	6528784	
	Examiner	Art Unit	
	Erik Kielin	3992	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The request for *ex parte* reexamination filed *16 September 2005* has been considered and a determination has been made. An identification of the claims, the references relied upon, and the rationale supporting the determination are attached.

Attachments: a)☐ PTO-892, b)☒ PTO-1449, c)☐ Other: _____

1. ☒ The request for *ex parte* reexamination is GRANTED.

RESPONSE TIMES ARE SET AS FOLLOWS:

For Patent Owner's Statement (Optional): TWO MONTHS from the mailing date of this communication (37 CFR 1.530 (b)). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

For Requester's Reply (optional): TWO MONTHS from the **date of service** of any timely filed Patent Owner's Statement (37 CFR 1.535). **NO EXTENSION OF THIS TIME PERIOD IS PERMITTED.** If Patent Owner does not file a timely statement under 37 CFR 1.530(b), then no reply by requester is permitted.

2. ☐ The request for *ex parte* reexamination is DENIED.

This decision is not appealable (35 U.S.C. 303(c)). Requester may seek review by petition to the Commissioner under 37 CFR 1.181 within ONE MONTH from the mailing date of this communication (37 CFR 1.515(c)). **EXTENSION OF TIME TO FILE SUCH A PETITION UNDER 37 CFR 1.181 ARE AVAILABLE ONLY BY PETITION TO SUSPEND OR WAIVE THE REGULATIONS UNDER 37 CFR 1.183.**

In due course, a refund under 37 CFR 1.26 (c) will be made to requester:

a) ☐ by Treasury check or,

b) ☐ by credit to Deposit Account No. _____, or

c) ☐ by credit to a credit card account, unless otherwise notified (35 U.S.C. 303(c)).

Erik Kielin
Primary Examiner
Art Unit: 3992

cc:Requester (if third party requester)

DECISION ON REQUEST FOR *EX PARTE* REEXAMINATION

A substantial new question of patentability affecting claims 1-9 of United States Patent Number US 6,528,784 B1 to Tang et al. is raised by the request for *ex parte* reexamination.

The References

J. M. **LAZAR** et al., "Design of a Time-of-Flight Mass Spectrometer as a Detector for Capillary Electrophoresis," *Analytical Chemistry*, 1997, vol. 69, no. 16, pp. 3205-3211.

R. D. **SMITH** et al., "Collisional Activation and Collision-Activated Dissociation of Large Multiply Charged Polypeptides and Proteins Produced by Electrospray Ionization," *J. Am. Soc. Mass Spectrom.*, 1990, vol. 1, no. 1, pp. 53-65.

M. V. **BUCHANAN** et al., "Continuous Octapole Electrospray Introduction System for FTICR," *46th ASMS Conference on Mass Spectrometry and Allied Topics*, May 31-June 4, 1998, p. 518.

B. **THOMSON** "Protein Charge Distribution Studies - From Droplet in Air to Ion in Vacuum" *44th ASMS Conference on Mass Spectrometry and Allied Topics*, May 12-16, 1996, p. 1092.

H. **KAMBARA** et al., "Collision-Induced Dissociation of Water Cluster Ions at High Pressure" *International J. Mass Spectrometry and Ion Physics*, 1977, vol. 25, pp. 129-136.

B. L. **KLEINTOP** et al., "Analyzing Thermally Labile Compounds in Electrospray Sources Using Heated Capillaries," *43rd ASMA Conference on Mass Spectrometry and Allied Topics*, May 21-26 1995 p. 905.

Patent US 6,015,972 to **HAGER**

Patent US 4,977,320 to **CHOWDHURY** et al.

Patent US 5,298,743 to **KATO**

Patent US 5,304,798 to **TOMANY** et al.

Prosecution History

During the examination of the application (09/715,815) that became the '784 patent, in the sole action on the merits (filed 14 March 2002), the examiner rejected all claims 1-9 over a single reference (WHITEHOUSE, US 5,652,427). Applicant commented and amended the claims in concert with the below remark,

> "Applicants have carefully studied U.S. Patent 5,652,427 [WHITEHOUSE] and admit that this patent shows a mass analyzer disposed in a high vacuum chamber

> for analyzing ions formed at or near atmospheric pressure and directed to the analyzer through intermediate vacuum chambers, and that **the sample ions travel through the chambers without fragmentation**."
>
> "Applicants' invention, however, is directed to the dissociation of adduct ions prior to entry into the mass analyzer, whereby they form sample ions which increase the sample ion current entering the mass analyzer. There is no teaching in this patent, nor would it have been obvious to one with ordinary skill in art at the time of the invention, to modify the Whitehouse patent in the manner required by the present claims. **There is no teaching of disassociating adduct ions to form sample ions which together with those sample ions which are not adducted with solvent molecules increases the ion current.**" (Applicant's Remarks filed 18 June 2002; emphasis added)

As noted in the Request in the paragraph bridging pages 7 and 8, the examiner of the '815 application stated reasons for allowance as follows:

> "The prior art searched and cited failed to teach or clearly suggest a mass spectrometer system and method for operating the said system including a mass analyzer disposed in a high vacuum chamber for analyzing sample ions formed at atmospheric pressure and directed to the analyzer through intermediate vacuum chambers in which **sample ions and solvent molecules form adduct ions with a reduction of sample ion current** as disclosed in claims 1 and 9. Claim 2 is allowable because of its dependency to claim 1. The prior art searched and cited failed to also teach or clearly suggest a method of mass analyzing sample ion produced at atmospheric pressure and introduce into a mass analyzer disposed in a vacuum chamber, and in which **some sample ions and solvent molecules combine to form adduct ion with a reduction of sample ions** as disclose in claims 3 and 4. Claims 5-8 are allowable because of their dependencies." (Notice of Allowance filed 6 September 2002; emphasis added)

SUBSTANTIAL NEW QUESTION OF PATENTABILITY

(1) The Request notes that the use of an API (atmospheric pressure ion) source such as electrospray ion source –an ion source explicitly disclosed in WHITEHOUSE -- inherently has the problem of the formation of adduct ions or cluster ions formed from the sample ion and weakly held solvent molecules and that the problem must be addressed (Request at pp. 12-13). The Request provides the quote from A. P. BRUINS, "Chapter 3: ESI Source Design and Dynamic Range Considerations" in R. B. Cole, Electrospray Ionization Mass Spectrometry, 1997 at p. 120.

> "In any design of an API mass spectrometer, the problem of the **formation of cluster ions** is addressed Polar molecules that tend to cluster with ions are water

> and solvent vapor present in air or generated by the evaporation of the eluate from a liquid chromatograph or electrophoresis instrument connected to the API source. **All** practical designs of API instruments are aimed at either prevention of clustering, or curing the problem by **breaking the cluster**." (Emphasis added.)

With this in mind, the above excerpt suggests that the design of the WHITEHOUSE spectrometer inherently takes into account the breaking of cluster ions because WHITEHOUSE uses an API ion source. While BRUINS was not applied in the Request to a proposed rejection of the '784 claims, given the examiner's reasons for allowance of the '815 application, and the fact the WHITEHOUSE teaches an API mass spectrometer admitted by Patent Owner to disclose all of the features except for the breaking of cluster ions without fragmentation in the ion guides (*supra*), the BRUINS teaching when considered with WHITEHOUSE raises a substantial new question of patentability. Furthermore there is a substantial likelihood that a reasonable examiner would consider this combined teaching important in deciding whether or not the claims are patentable.

(2) The Request (pp. 10-12) indicates that Requester considered claims 1, 2, and 4-9 obvious over LAZAR in view of SMITH, and over HAGAR in view of LAZAR.

Neither LAZAR nor SMITH was present during the examination of the '815 application that became the '784 patent. While HAGAR is "old art," a substantial new question of patentability is not precluded when "old art" may be considered anew with new art, e.g. LAZAR.

The Request notes at page 26 (right-hand col., first box) that LAZAR discloses the formation of adducts in one of the experiments discussed therein, with LAZAR stating, "However the paraquat spectrum was mainly compose of a series of **ion clusters**. The signal intensity at 93 m/z was extremely weak and **dependent on the first quadrupole offset voltage**" (p. 3208; emphasis added). Accordingly, LAZAR disclose not only the formation of the cluster ions, but also the implicit or inherent breaking of the sample ion from the cluster ion without fragmentation, as dictated by the "first quadrupole offset voltage."

Additionally, the Request indicates at p. 27 (right-hand col., first box) that SMITH teaches conversion of solvent adduct ions by application of a DC offset voltage between an orifice and an ion guide in the range of 5-40 V in a pressure environment similar to that in the second ion guide chamber of LAZAR (Smith at page 56, left-hand col.).

LAZAR considered with SMITH explicitly discloses, *inter alia*, the feature believed by the examiner of the '815 application to make at least independent claims 1, 4, and 9 of the '784 patent allowable. Accordingly, there is a substantial likelihood that a reasonable examiner would consider this teaching important in deciding whether or not the claims are patentable, and Examiner agrees that a substantial new question of patentability exists as to claim 1, 2, and 4-9 over the combined teaching of LAZAR with SMITH.

(3) The Request (p. 10) indicates that Requester considered claims 1, 2, and 4-8 obvious over HAGAR in view of LAZAR

HAGER, although of record, was never commented on by the examiner of the '815 application. As noted in the Request at p. 28 (right-hand col., first box), HAGER discloses that "ions generated by electrospray ionization techniques may enter the vacuum chamber as monomers, **monomers clustered with solvent molecules**, and possibly **multimers with** and without **solvent molecules**" (col. 10, lines 45-48; emphasis added). Accordingly, HAGER teaches the formation of cluster ions. The request also notes that HAGAR states, "**various stages of declustering** are **commonly used** to reduce this mixture of ionic species to a **larger proportion of bare monomer ions to solvated ions**. Conventional declustering methodologies include... collisional dissociation by acceleration of the ions through relatively high pressure regimes using **voltage gradients** between the orifice and skimmer and **between the skimmer and Q0**" (col. 10, lines 51-56; emphasis added). Accordingly, HAGER additionally teaches "various stages" of breaking of the sample ion from the cluster using a DC offset between the skimmer and the ion guide.

When considered with the mass spectrometer system of LAZAR, the combination of HAGER with LAZAR raises a substantial new question of patentability of claims 1, 2, and 4-8 for disclosing a feature believed by the examiner of the '815 application to make at least independent claims 1 and 4 of the '784 patent allowable. Furthermore there is a substantial likelihood that a reasonable examiner would consider this teaching important in deciding whether or not the claims are patentable.

(4) The Request at pages 10-12 indicates that Requester believes claims 1, 2, and 4-9 to be obvious over BUCHANAN in view of either of SMITH and THOMSON. For the reasons indicated above, HAGER is believed to raise a substantial new question of patentability as to claim 9 of the '784 patent.

BUCHANAN teaches a triple quadrupole ion guide, each with separate chambers and pressures, the pressure decreasing in each from the electrospray ion source toward the mass analyzer. BUCHANAN also teaches varying the potential on the skimmer and each of the octapole rods.

As noted above, SMITH teaches conversion of solvent adduct ions by application of a DC offset voltage between an orifice and an ion guide in the range of 5-40 V in a pressure environment similar to that in the third chamber ion guide chamber of BUCHANAN (octapole #3). Accordingly, the combination of BUCHANAN with SMITH raises a substantial new question of patentability as to claims 1, 2, and 4-9 of the '784 patent. Furthermore there is a substantial likelihood that a reasonable examiner would consider this teaching important in deciding whether or not the claims are patentable.

Alternatively THOMSON teaches the use of a triple quadrupole mass spectrometer wherein the second quadrupole (Q2) is used for "declustering" clustered ions without fragmentation is some examples by using an offset voltage between a preceding lens and Q2. Accordingly, the combination of BUCHANAN with THOMSON raises a substantial new question of patentability as to claims 1, 2, and 4-9 of the '784 patent. Furthermore there is a substantial likelihood that a

reasonable examiner would consider this teaching important in deciding whether or not the claims are patentable.

(5) The Request at p. 10 indicates that Requester believes claim 3 to be anticipated by each of the following references listed above: SMITH, KAMBARA, CHOWDHURY, KATO, KLEINTOP, THOMSON, TOMANY, and HAGER.

None of SMITH, KAMBARA, CHOWDHURY, KATO, KLEINTOP, THOMSON, and TOMANY was present during the examination of the '815 application that became the '784 patent.

Claim 3 of the '815 application was amended by Applicant to read,

> 3. A method of mass analyzing sample ions produced at atmospheric pressure[, in which adduct ions are formed,] and introduced into a mass analyzer disposed in a vacuum chamber, and in which some sample ions and solvent molecules combine to form adduct ions with a reduction of sample ions comprising the step of dissociating the adduct ions prior to entry into the mass analyzer to form sample ions to increase the [analyte] sample ion current entering into the mass analyzer.

The underlined portion is added while the bracketed portion was removed.

As noted in the Request at p. 32 (right-hand col., 1st and 2nd boxes), SMITH teaches the formation of adduct/cluster ions as well as the use of a DC offset voltage between the orifice and the ion guide to accelerate the cluster ion and thereby dissociate it into sample ions and solvent (p. 56, left-hand col.). Accordingly SMITH raises a substantial new question of patentability of claim 3 of the '784 patent.

Similarly, each of KAMBARA (p. 130, Fig. 1 and p. 135), CHOWDHURY (col. 2, lines 19-24 and col. 3, lines 54-58), KATO (col. 4, line 61 to col. 5, line 6 and col. 7, lines 18-28), KLEINTOP (p. 905, Fig. 2b), THOMSON (p. 1092), and TOMANY (col. 5, lines 11-19 and lines 26-37) teaches both the formation and dissociation of cluster ions without fragmentation by the acceleration of cluster ions through ion guides and therefore raises a substantial new question of patentability as to claim 3 of the '784 patent. Furthermore there is a substantial likelihood that a reasonable examiner would consider each of these teachings important in deciding whether or not claim 3 is patentable.

HAGER is old art. The substantial new question of patentability of claim 3 is based solely on a patent already cited in an earlier concluded examination of the patent being reexamined. On November 2, 2002, Public Law 107-273 was enacted. Title III, Subtitle A, Section 13105, part (a) of the Act revised the reexamination statute by adding the following new last sentence to 35 U.S.C. 303(a) and 312(a):

> "The existence of a substantial new question of patentability is not precluded by the fact that a patent or printed publication was previously cited by or to the Office or considered by the Office."

For any reexamination ordered on or after November 2, 2002, the effective date of the statutory revision, reliance on previously cited/considered art, i.e., "old art," does not necessarily preclude the existence of a substantial new question of patentability (SNQ) that is based exclusively on that old art. Rather, determinations on whether a SNQ exists in such an instance shall be based upon a fact-specific inquiry done on a case-by-case basis.

While HAGER was present before the examiner during the examination of the 10/166,718 application, the reference was not relied on to reject the claims. When a substantial new question of patentability is raised solely over previously cited art, the Court stated in the sole footnote, in *In re Robert T. Bass*, 314 F.3d 575, 576-77, 65 USPQ2d 1156, 1157 (Fed. Cir. 2002), in pertinent part,

> "37 CFR 1.2 requires that all Office business be transacted in writing. Thus, the Office cannot presume that a prior art reference was previously relied upon or discussed in a prior Office proceeding if there is no basis in the written record to so conclude other than the examiner's initials or a check mark on a PTO 1449 form, or equivalent, submitted with an information disclosure statement. Thus, any specific discussion of prior art must appear on the record of a prior related Office proceeding."

Accordingly, because no written consideration of HAGER exists of record, a substantial new question of patentability is not precluded.

As noted above HAGER teaches both the formation and dissociation of cluster ions without fragmentation by the acceleration of cluster ions through ion guides and therefore raises a substantial new question of patentability as to claim 3 of the '784 patent. Furthermore there is a substantial likelihood that a reasonable examiner would consider these teachings important in deciding whether or not claim 3 is patentable.

(6) The Request at pages 11-12 indicates that Requester believes claim 9 to be anticipated or obvious over HAGER. For the reasons indicated above, HAGER is believed to raise a substantial new question of patentability as to claim 9 of the '784 patent.

Note, **because a substantial new question of patentability exists as to at least one claim, all claims will be examined**.

Conclusion

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that reexamination proceedings "will be conducted with special dispatch" (37 CFR 1.550(a)). Extension of time in reexamination proceedings are provided for in 37 CFR 1.550(c).

After the filing of a request for reexamination by a third party requester, any document filed by either the patent owner of the third party requester must be served on the other party (or parties where two or more third-party-requester proceedings are merged) in the reexamination proceeding in the manner provided in 37 CFR 1.248. See 37 CFR 1.550(f).

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. US 6,528,784 B1 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Please mail any communications to:

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Any inquiry concerning this communication or earlier communications from the Reexamination Legal Advisor or Examiner, or as to the status of this proceeding, should be directed to the Central Reexamination Unit at telephone number (571) 272-7705.

Signed:

Erik Kielin
Primary Examiner
Central Reexam Unit 3992
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November 3, 2005

Conferees:

SPRE 3992

SJC 11-3-2005